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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,389	09/14/2005	Shigeru Kanaoka	091228	2212

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EXAMINER	
BABIC, CHRISTOPHER M	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
02/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentmail@whda.com

Office Action Summary	Application No.	Applicant(s)	
	10/549,389	KANAOKA, SHIGERU	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,15-18,20,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,15-18,20,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *SEQ NOTICE TO COMPLY*.

DETAILED ACTION

Status of the Claims

Claim(s) 5, 15-18, 20, 22, and 23 are pending and under examination. The following Office Action is in response to Applicant's communication dated November 19, 2009. The following Office Action is NON-FINAL due to the new grounds of rejection presented below.

Examiner of Record

As an initial matter, it is noted that the examiner of record has been changed from Suchira Pande, Art Unit 1637, to Christopher M. Babic, Art Unit 1637.

Sequence Rules Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

Applicant is given time of reply to this office action within which to comply with the sequence rules, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in **abandonment** of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Page 9 contains sequences without SEQ ID NOs. If these sequences are included in the sequence listing provide by Applicant, the specification should be amended to include the SEQ ID NOs. If these sequences were not included in the sequence listing filed September 14, 2005, Applicant should provide a substitute sequence listing and a CRF that include those sequences.

Claim Rejections - 35 USC § 112 - Indefiniteness - New Grounds

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 15-18, 20, 22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claimed invention is rejected as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a recitation of the correlation between the degree of expression of the recited gene and the likelihood of having colon cancer. Applicant is directed to the recent Federal Circuit decision *Griffin v. Bertina*, 62 USPQ2d 1431 (Fed. Cir. 2002), in which the court found that a "wherein" clause reciting the correlation between the presence of a nucleic acid mutation and an increased risk of developing a disease related back to and clarified what is required by a preamble that recited a method of diagnosing an increased risk of developing such disease thereby giving meaning and purpose to the manipulative steps, expressly noting:

> "Furthermore, the Board did not err in giving limiting effect to the “wherein” clauses because they relate back to and clarify what is required by the count. Each “wherein” clause refers to the point mutation, giving meaning and purpose to the manipulative steps. The first “wherein” clause expresses the inventive discovery of the correlation between the point mutation and APC resistance, i.e., that the presence of the point mutation causes an increased risk of thrombosis. The second “wherein” clause

elaborates the meaning of the preamble, indicating that the point mutation correlates with a decrease in the degree of inactivation of human Factor V and/or human Factor Va by APC (i.e., increased APC resistance), and hence an increased risk of thrombosis. The manipulative steps set forth in the count have little meaning or utility unless they are placed within the context of the diagnosis of an increased risk of developing thrombosis, recited in the preamble and "wherein" clauses. Griffin cites other cases in which the court determined that "whereby" clauses were nonlimiting. Aside from the fact that "wherein" is an adverb and "whereby" is a conjunction, those cases are all fact-specific, and what is clear here is that the "wherein" clauses are a necessary part of this count."

It is noted that an amendment introducing a "wherein" clause analogous to that presented in the count discussed in *Griffin v. Bertina* would obviate the instant grounds of rejection.

Claim Rejections - 35 USC § 112 –Enablement - New Grounds

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 5, 15-18, 20, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of "confirming a diagnosis of colon cancer in a human patient" based solely on the detection of COX-2 gene expression, does not reasonably provide enablement for absolute detection of colon cancer in any species based solely on the detection of COX-2 gene expression of any degree.

Enablement Issues

The specification does not enable the claimed invention for: 1) absolute detection of colon cancer based solely on detection of any degree of COX-2 gene expression; or 2) any degree of detection of colon cancer in any species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The Nature of the Invention

The claimed invention is drawn to disease detection based solely on gene expression. The inventions are in the class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth of the Claims

The claims are drawn to absolute detection of colon cancer in any species (e.g. apes, mice, fruit flys, etc.) based solely on COX-2 gene expression.

Quantity of Experimentation

Disease detection based on gene expression is an inventive, unpredictable, and difficult undertaking that needs to be demonstrated in a variety of patients with a statistically significant result. This requires in some cases years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The Unpredictability of the Art and the State of the Prior Art

The art is replete with evidence demonstrating the unpredictable nature of gene expression-based disease correlations and their unreliability with respect to disease diagnosis and model organisms.

With regard to definitive diagnosis of disease based solely on gene expression, a review article by Murphy et al. entitled "Gene expression studies using microarrays: principles, problems, and prospects," (Adv Physiol Educ. 2002 Dec;26(1-4):256-70) asks the question, "How do the expression patterns of these genes change as a consequence of physiological cues and disease (pg. 257)? " and ultimately concludes that:

"The microarray-based approach to the problem of gene function clusters genes according to their expression behavior under defined conditions and to assign function. The hypothesis of this "guilt-by-association" approach is that clustered genes may be co-regulated and therefore may be involved in similar functions. However, sequence and expression analysis alone is insufficient to fully inform us about gene function. To make sense of these data, the hypotheses that emerge from analysis of systemic expression information must be tested empirically. This will involve the integration of genomic knowledge with biochemistry, cell biology, genetics, structural biology, and proteomics. Ultimately, hypotheses must be tested within the physiological integrity of the whole organism. This will demand the development of a new, high-throughput systems biology coupled with rapid and efficient gene transfer techniques (pg. 268)."

These conclusions are in agreement with that of Lucentini, who entitled an article, "Gene Association Studies Typically Wrong" (*The Scientist*, 18(24):20) and highlights that:

"Experiences like Crocq's, in which follow-up studies overturn an initial finding of a gene-disease association, are strikingly common, researchers say. Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated (pg 3 printout)."

With regard to gene expression correlation across species, Grigoryev et al. (Genome Biol. 2004;5(5):R34. Epub 2004 Apr 27) provides an experiment testing gene expression of homologous genes from the rat, mouse, dog, and human genomes under the same environmental conditions (Table 4, microarrays U133, U95, U74, and U34, for example). Such testing revealed variable fold-change expression levels of single genes from species to species (pg. R34.9, Table 4, IL-13 detected on U133 and U34, but not on U95 and U74; CCL2 detected on U95, U74, and U34, but not on U133, for example).

Turning to Applicant's own results, COX-2 expression was not detected in 100% of colon cancer patients (example 1, 27 out of 30, for example). Furthermore, Applicant provides no analysis indicating that the results are statistically significant. And perhaps the most significant, Applicant provides no data indicating that a patient is confirmed as having colon cancer solely on the basis of COX-2 gene expression, i.e. all patients

tested were known to have colon cancer prior to testing.

Thus, a person of ordinary skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains.

Working Examples

Applicant provides examples of the claimed invention in human patients diagnosed with colon cancer.

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Guidance in the Specification

Applicant provides no evidence that the results in the specification are indicative of an absolute detection method, or applicable to species other than human.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance in the specification, the lack of a working example which addresses analysis in patients not diagnosed with colon cancer or species other than humans and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102 - Withdrawn

Upon further consideration, the rejection of claim(s) 5, 17-18, 20, 22, and 23 over Chapkin has been withdrawn. Neither Chapkin nor the instant invention is enabled for absolute detection of colon cancer based solely on the detection of COX-2 expression.

Claim Rejections - 35 USC § 103 - Withdrawn

Upon further consideration, the rejection of claim(s) 5, 17-18, 20 and 23 over Alexander & Raicht, Shattuck-Brandt, and Lagerholm has been withdrawn. None of the cited references are enabled for absolute detection of colon cancer based solely on the detection of COX-2 expression. With regard to Applicant amending the claimed invention to a method "for confirming the diagnosis of colon cancer," is noted that the current examiner has reviewed the previous prosecution and Applicant's arguments dated November 19, 2009 with respect to the previous rejection based on Alexander & Raicht, Shattuck-Brandt, and Lagerholm, and agrees with the previous examiner that such references provide sufficient teachings for establishing grounds for an obviousness rejection based on simple detection of COX-2 gene expression. With specific regard to the assertion of unexpected results (see remarks dated November 19, 2009 pg. 13-17), Applicant is reminded that, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re*

Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) In the instant case, Applicant must provide sufficient evidence that a certain degree of gene expression provided unexpected results.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 814-880-9945. The examiner can normally be reached on Monday-Friday 10:00AM to 6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher M. Babic/
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